Review Article

Current Trends in SNP Analysis with Special Reference to Candidate Genes Associated with Reproduction Traits

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Rec. Date:	Feb 27, 2018 10:00
Accept Date:	Apr 09, 2018 16:32
DOI	10.5455/ijlr.20180227100002

Abstract

The genetic improvement programmes for large animals through progeny testing and pedigree selection are proven methodology for achieving a fixed genetic progress, but these are time consuming and costly. Marker Assisted Selection (MAS) is an innovative tool in animal breeding and has great potential to complement or replace the traditional breeding programme. Single Nucleotide Polymorphism (SNP) are the most common type of genetic variation in the genome. Reproductive performance is a good determinant of productivity and sustainability in farm animals. Reproduction traits determining productive life and culling decisions in dairy herds. Many SNPs have been found to be associated with reproduction traits. There are mainly two types of methods for detection of SNP genotyping: (1) traditional gel-based method and (2) high throughput method. Detection of DNA markers associated with improved reproductive performance through genome wide association studies could lead to genetic gain that is more balanced between fertility and production.

Key words: Single Nucleotide Polymorphism, Marker Assisted Selection, Candidate Genes, Reproduction Traits

How to cite: Parmar, G., Gupta, J., Chaudhari, J., Prajapati, B., & Sathwara, R. (2018). Current Trends in SNP Analysis with Special Reference to Candidate Genes Associated with Reproduction Traits. International Journal of Livestock Research, 8(9), 12-24. doi: 10.5455/ijlr.20180227100002

Introduction

In order to ensure optimum dairy production, genetic improvement in the functional traits like reproduction, longevity and health of animals etc. is strongly needed. The genetic improvement programmes for cattle and buffalo through progeny testing and pedigree selection are proven methodology to achieve a fixed genetic progress in the livestock population. However, these methods are time consuming, complex, tedious and costly. Marker assisted selection (MAS) considered to be an innovative tool in animal breeding, has great potential to complement or replace the traditional breeding programme (Swaminathan and Pande,

2015). Genetic markers can take a number of forms and in the simplest definition these are an observable genetically controlled variation that follow a Mendelian pattern of inheritance (Williams, 2005). For achieving faster genetic progress, genetic markers can be amalgamated with the breeding programme. The process of choosing a particular animal for a particular trait using genetic markers is called MAS.

Livestock sector plays a vital role in the life of farmers. It provide food, income, employment and many more essential by-products for development of rural economy. Reproductive efficiency of an animal is of paramount importance when profitability of a dairy farm is assessed. There are several factors that cause decrease in reproductive efficiency like, late age of maturity leading to high age at first calving, longer calving interval and longer dry period. Due to increased calving intervals, incomes of farmers will be reduced (Seegers, 1994). Owing to mentioned factors, the farm income is affected by the reduction in milk production as well as less number of calves produced by the animals. Reproductive traits in dairy cattle are not only a measure of fertility but also of productivity and production potential of an animal for life (Royal, 2000). Longer calving intervals are usually associated with longer dry periods (Kuhn *et al*., 2005). Dairy industry incurs heavy loss due to reduced reproductive rate, prolonged calving interval, drop in milk production, reduced calf crop and early depreciation of potentially used animals (Lobago *et al.,* 2006). Reproductive performance of the animal also depends on the management adopted by the farmers as well as their knowledge and skills. Since heritability of the reproductive traits is in general very low, genetic tool like MAS will be of great importance. Traditional breeding methodology greatly utilise the heritable variation present in a population for a particular trait therefore, traits having low heritability will yield less improvement. Genotyping allows for the accurate detection of specific DNA variations that have been associated with measurable effects on complex traits. Generation intervals were suggested to drop from around 5 to 6 years in traditional dairy cattle breeding programs to around 1.5 years when using such genetic markers (Pryce and Daetwyler, 2012).

A marker is usually considered as a constituent that determines the function of a construction. Genetic marker can be defined as any stable and inherited variation that can be measured or detected by suitable method and can be used subsequently to detect the presence of a specific genotype or phenotype other than itself, which otherwise is not measurable or very difficult to detect (Vignal *et al*., 2002). These variations can be morphological, chromosomal and biochemical markers etc. On the basis of techniques used for detection, these markers are classified into two main categories, *viz*. hybridization based marker and PCR based marker. Hybridization based marker include traditional RFLP (Restricted Fragment Length Polymorphism) analysis where, appropriately labelled probes for structural genes are used. Hybridization can also be carried out with the probe for the different families of hypervariable tandem repeats (Schork *et al.,* 2000). PCR based marker is that marker in which target sequence of a particular fragment is amplified using specific primer. PCR based markers includes PCR-RFLP and SSRs (Simple Sequence Repeats). In

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arbitrary PCR assay, a randomly designed single primer is used to amplify the sequence and it is called as RAPD (Random Amplified Polymorphic DNA). Single Nucleotide Polymorphism (SNPs) are currently the marker of choice due to their large numbers in virtually all population of individuals. SNP marker is just a single base change in a DNA sequence, with a usual alternative of two possible nucleotides at a given position (Gupta *et al*., 2001). SNP discovery has been described based on the comparison of locus-specific sequences generated from different chromosomes. The simplest (when target is a defined region of candidate genes) is to perform direct sequencing of genomic PCR products obtained in different individuals (Vignal *et al*., 2002).

Genetic and environmental factors are known to influence production traits in dairy cattle. Selection of animals with higher production or better reproductive performance is of great significance to breeders and consumers. Current technologies enable scientists to improve upon the accuracy and efficiency of traditional selection methods by applying genetic markers through marker-assisted selection. Therefore, those genetic polymorphisms which are significantly associated with certain traits of economic importance are very useful. Detection of polymorphisms in genes associated with production and reproduction traits and the identification of the allele which results in a phenotype of interest can allow for marker assisted selection (Zhao *et al*., 2004; Gutierrez *et al*., 2008).

Marker Assisted Selection (MAS)

Molecular marker is a fragment of DNA that is associated with certain location within the genome. The process of selection for a particular trait using genetic marker is called Marker Assisted Selection. In molecular genetics, in terms of the type of information they provide at a single locus, DNA markers can be described in to three main categories, *viz.* Bi-allelic dominant: Such as RAPDs (Random Amplification of Polymorphic DNA), AFLPs (Amplified Fragment Length Polymorphism); Bi-allelic co-dominant: Such as RFLPs (Restriction Fragment Length Polymorphism), SSCPs (Single Stranded Conformation Polymorphism) and Multi-allelic co-dominant: Such as the microsatellites (Vignal *et al*., 2002).

A DNA polymorphism is any difference in the nucleotide sequences between individuals, these differences can be single base pair changes, any deletions or insertions and even changes in the number of copies of a given DNA sequence. The most studied DNA polymorphisms are, restriction fragment length polymorphisms (RFLP), microsatellite and single nucleotide polymorphism (SNP). RFLP is a method first identified by Grodzicker *et al*. (1974). Here, sample of the DNA are cut with restricted endonuclease enzymes. A specific restricted enzyme cut the DNA sample at the particular site. The resulting DNA fragments are then separated on the basis of various length through a gel electrophoresis process and separated fragments are hybridized with radioactive or chemi-luminescent homologous probes which is exposed to an X-ray film. After that different fragments which are visible by autoradiography (Yang *et al.,*

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2013). Similarly, microsatellite DNA, also known as simple sequences repeats (SSRs) or short tandem repeats (STRs). These are common repeated sequences within eukaryotic genomes. Generally, they are made up of 1–6 base pairs (bp) tandem repeats, repeated several times (e.g. CACACACACACACACA) (Litt and Luty, 1989; Tautz., 1989).

In 1996, Eric S. Lander proposed a new molecular marker technology named single nucleotide polymorphism. These markers involve the substitution of one nucleotide for another, or the addition or deletion of one or a few nucleotides. They are stable sequence variations, in which typically two alternate nucleotide bases are found to be located at one position across some population. Even though most of the SNPs do not have observable phenotype but they occur in enough frequency within the genome to be associated with certain traits. Thus, they are effective markers for genomic research (Zhen and Altman, 2004). Microsatellite loci often encounter with the problem of absence of any allele and mutation patterns that are variable, hence it need complex data analysis. Whereas, mutations observed as SNPs are abundant and widespread in genomes of many species at coding and non-coding regions.

Genetic variation is a variation in alleles of genes in a gene pool or variation in the DNA sequence in each genome. There are mainly three different types of genetic variations namely, Single nucleotide polymorphisms (SNPs), Multi-nucleotide polymorphisms (MNPs) and Microindels. More than 3 million SNPs are located in the human genome (International HapMap Consortium 2005, Levy *et al*., 2007). The frequency of DNPs and TNPs, the most common forms of MNPs, amounts to approximately 1% of the total number of SNPs (Rosenfeld *et al*., 2010). SNPs are divided into two main categories; linked SNPs, are those SNPs that do not reside within genes and do not affect protein function and causative SNPs, affect the way a protein functions. Further, causative SNPs are present in two forms namely, coding SNPs (located within the coding region of a genes, can change the amino acid sequence of the genes protein product) and non-coding SNPs (located within the gene's regulatory sequences, change the timing, location or level of gene expression). The coding SNPs can further be synonymous (do not affect the protein sequence) and non-synonymous (change the amino acid sequence of protein). Non-synonymous SNPs can be either missense (a point mutation in which a single nucleotide change results in a codon that codes for a different amino acid) or nonsense (point mutation in a sequence of DNA that results in a stop codon).

How SNPs are being discovered?

SNP discovery is the process of finding the polymorphic sites in the genome of the species and populations of interest. Much of the SNP discovery has been done *in silico*, meaning that genomic information from multiple individuals in the public databases is screened for the identification of putative polymorphisms

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(Phillip *et al.,* 2004). There are mainly two steps that are employed for detection of SNP markers; locus discovery and genotyping. Although many of the technologies are available for both of these steps, the methods used are generally selected based on criteria for the particular study to be performed.

Reproductive Traits and their Association with SNPs

Reproductive performance is a good determinant of productivity and sustainability in farm animals (Olsen *et al*., 2011). There is direct association among the first oestrous and number of services for conception, service period and calving intervals. Time of service is mostly influenced by features comprising the parturition, kind of management and calving season (Imran *et al.,* 2014). The service period is directly associated to calving interval. When the service period is extended, the calving interval is also extended, leading to the longer gestation period. The service period is negatively associated to average milk yield of animal. Service period of about 60-80 days is considered to be highly desirable. For the determining productive life and culling decisions in dairy herds based on some of the traits like age at first calving, calving interval and lactation length (Hare *et al.,* 2006).

SNPs Associated with AFC

The period that a cow needs to reach its maturity and to reproduce for the first time is referred to as age at first calving (Raden and Klaaskate, 1993). However, reproductive traits, such as age at first calving (AFC), have a huge impact on profitability in the dairy industry. AFC is easy and inexpensive to measure, and it can be used as an indicator of fertility. According to Martin *et al*. (1992), indigenous cows (*Bos indicus*) generally take longer to reach puberty than exotic (*Bos taurus*).

Table 1: SNPs of candidate genes associated with AFC

Gene	SNP name	Location (Chromosome)	Reference
CALCRL	*rs133983601*	2	Li *et al*. (2008)
ANTXR2	*rs135323951*	6	Reeves *et al.* (2012)
FGF5	rs135323951	6	Nilsson *et al.* (2001)
PRDM8	rs135323951	6	Utsunomiya *et al.* (2014)
GHR	rs41639259	20	Komisarek *et al.* (2011)

Characterizing genomic regions explaining differences in AFC may contribute to the early identification of animals. Detection of DNA markers associated with improved reproductive performance through genome wide association studies could lead to genetic gain that is more balanced between fertility and production (Olsen *et al.,* 2011).

CALCRL gene, affecting the secretion of estradiol and progesterone and consequently the activation and growth of primordial follicles (Li *et al*., 2008). This phenomenon can be related with the onset of reproductive life in cows and directly affect AFC. So, CALCRL gene seems to be involved in reduction of

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AFC. *ANTXR2* gene is associated with a rare disorder named Infantile Systemic Hyalinosis (ISH), which may retard intrauterine growth (Reeves *et al.,* 2012). So ANTXR2 gene increase AFC. *FGF5* belongs to the family of fibroblast growth factors (FGF). This family of genes is closely linked to the development of the primordial and primary follicles. Nilsson *et al.* (2001) found that FGF in oocytes promote growth of granulosa cells during early follicular development. FGF5 gene supposed to be associated with reduction of AFC. Marker (SNP) rs135323951 is associate with PRDM8 gene which are affect the AFC. Genes (*CALCRL*, *ANTXR2* and *FGF5*) have important roles for the development of primordial germ cells as well as reproductive organs.

SNPs Associate with Calving Interval

Few genes were found surrounding the *rs41888601* on chromosome 18. Majority from these genes are related with metal ion transporter gene families. SMG9 is one of the important gene of them. *SMG9* is involved in nonsense-mediated mRNA decay (*NMD*). *NMD* selectively degrades premature termination codon (PTC) containing mRNAs (Izumi *et al*. 2012). According to Trevisol *et al*. (2013), the luteolysis process causes an increase in the immune cell levels. Thus the retarded effect on immune cell maturation can affect the luteolysis process, interfering in the oestrus cycle and calving interval. Marker *rs137830830* associated with *SLC39A11* and *SOX9*. *SLC39A11* is gene involved in metal ion transporter family means mainly selenium content is present. Selenium have a positive effect on fertility (Mehdi *et al*., 2013). The *SOX9* is also well known and it is related with sex-determining and gonad-formation (Harley *et al.,* 2013).

Table 2: SNPs of candidate genes associated with calving interval

Gene	SNP name	Location (Chromosome)	Reference
SMG9	rs41888601	18	Izumi *et al*. (2012)
SLC39A11	rs137830830	19	Machado *et al.* (2014)
SOX9	rs137830830	19	Machado *et al.* (2014)
EPGN	rs43470290	6	Raven *et al.* (2015)

SNPs are most commonly used, because it is possible to genotype individuals for 1 million of SNPs at reasonable cost. Earlier methods of MAS, which relied on identifying a small number of causal variants, were not successful for complex traits because most of these are affected by hundreds or thousands of polymorphism, each with small effects. Traditional selection (based on progeny and phenotype alone) is time consuming, where as in case of genomic selection, animals can be selected accurately early in life, based on their genomic predictions and for traits that are difficult or expensive to measure (e.g. fertility, FCR, disease resistance). In traditional method, generation interval is 5-7 years or longer, but in case of genomic selection GI is reduced to 2 years with increased rate of genetic gain.

Methods of SNPs Detection

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SNPs genotyping is performed traditionally by gel-based but recent development has led to the development of many high throughput techniques. Amplification Refractory Mutation System (ARMS) technique is mostly used for the identification of unknown mutations which was first described by Newton *et al.* (1989). The method relies on allele specific PCR and two different forward primers are designed with differing nucleotides to complement the two expected alleles (Dearlove, 2002). Restriction fragment length polymorphism (RFLP) is classical technique invented in 1984 by the English scientist Alec Jeffreys, used for the known mutations and single change in nucleotide sequence. If the change results in the creation or abolition of a restriction endonuclease recognition site, then the DNA sequence acquires or loses the ability to be cleaved by a particular restriction endonuclease. The digestion with the appropriate restriction enzyme generates a long fragment when recognition site is absent and vice versa (Beuzen *et al*., 2000). Single strand confirmation polymorphism is another classical technique for the detection of unknown SNPs and mutations in DNA fragments on the basis of changes in secondary structures in ss-DNA caused by a change in sequence. The technique is cost effective, easiest and having high mutation detection rate (70-95%). Some factors like concentrations of DNA template and primers, running temperature and time may affect the detection of mutations and reproducibility (Shojaei *et al*., 2010). The differences in nucleotide, which are detected as alterations in the DNA molecule mobility by gel electrophoresis and the banding patterns are visualized and compared with the controls of known variants (Orita *et al*., 1989).
Denaturing high performance liquid chromatography (DHPLC) is another relatively new and one of the most powerful techniques. DHPLC detect the mutations with the formation of heteroduplex between normal and mutated DNA strands. The normal DNA fragment includes target DNA containing the SNP polymorphic site and an allele-specific DNA sequence. Fragments are denatured, if step by step temperature is increased, then slow cooling is done and is allowed to gradually re-anneal. At the higher temperature the DNA fragments are separated, partial melting occurs and the heteroduplex DNA containing mismatches will have a different retention time than the homoduplex DNA. The mismatched heteroduplexes will have a different melting temperature than the homoduplexes and will not be retained in the column as long. This tool is time consuming and also as optimum assay temperature for each of the targets has to be determined (Bhattaramakki and Rafalski, 2001). Temperature determines sensitivity, and its optimum can be predicted by computation (Oefnerand Xiao, 2001).
Recent efforts are directed towards the development of high throughput methods which are broadly divided in to Allele Discrimination and Assay Chemistry methods. One Allele discrimination method is the Allele-Specific Hybridization technique which uses Taq DNA polymerase. This method is based on the characteristic 5' to 3' exonuclease activity of Taq DNA polymerase (Holland *et al.,* 1991; Livak *et al.,* 1995). The probes consist of a 5' reporter dye and a 3' quencher dye. The hybridization is reduced between the probe and target DNA sequence, when disparity between them. As a result, cleavage of reporter from

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quencher is stopped and releases the fluorescent signal. Single-Base Primer Extension also known as mini-sequencing. It is a very tough and highly flexible allelic discrimination mechanism. This technique, require the smallest number of primers or probes. Products covering the SNP region are amplified by the PCR, and any remaining amplification primers and dinucleotide triphosphates are inactivated or removed before to mini sequencing (Syvanen, 1999). The primer is then extended for one or several nucleotides to including the SNP region.

Among the Assay Chemistry methods, Flap Probe Cleavage Approach is a molecular mechanism for single base detection based on the observation that flap endonucleases and cleave a structure formed, when two overlapping oligonucleotides hybridize to a complementary DNA target. When the downstream oligonucleotide is designed with a 'flap' consisting of non-complementary sequence, this stretch of DNA is cleaved in the presence of an upstream 'invader' oligonucleotide and target DNA. If the cleaved 'flap' is used as the 'invader' oligonucleotide in a secondary assay with a second 'flap' probe and a synthetic template, one can amplify the signal without amplifying the genomic SNPs genotyping and genomic selection in farm animal's DNA target. The final detection can be based on change in intensity of fluorescence when the fluorescence resonance energy transfer (FRET) probe is cleaved (Lyamichev *et al.,* 1999). Another such method is Oligonucleotide Ligation Assay (OLA) which was first described by Landegren *et al*. (1988). According to Tobe *et al*. (1996), the assay is performed by designing two oligonucleotides specific for each allele. The ligation of two oligonucleotides, hybridized to a DNA template, one of which is allele specific such that it will only form part of a ligated product if it is complimentary to the target sequence (Jenkins and Gibson, 2002). For the OLA, two primers are designed that are directly next to each other when hybridized to the complementary target DNA sequence in question. The two adjacent primers must be directly next to each other with no interval, or mismatch, for them to be covalently joined by ligation (Dearlove, 2002).

DNA microarray is high throughput, quite expensive and complex method of SNP detection. DNA chips and microarrays of immobilized oligonucleotides of known sequences, which differ at specific sites of individual nucleotides (at the site of SNP), are used for the detection of SNPs. These arrays are based on the ability of complementary strands of DNA (or DNA and RNA) to hybridize to one another in solution with high specificity. DNA chip contains thousands of probes and c-DNA bound with consequence probes. Four oligonucleotides in a column of an array differ only at the SNP site and only one would be fully homologous. When such an array is hybridized with the PCR product, the perfect match allows the binding and mismatched products would be washed away. The perfect match in each case can be detected through a detection system (Gupta *et al.,* 2001).

Pyrosequencing is a DNA sequencing technology which uses DNA polymerase in a sequencing reaction for SNP detection, but the reaction proceeds beyond one nucleotide to provide pyrosequencing users with

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short-run sequencing data around their SNPs (Ronaghi *et al*., 1998). DNA polymerase, ATP sulfurylase, Luciferase and apyrase enzymes are used in pyrosequencing. A sequencing primer positioned upstream of the SNP site is incubated with amplified target sequence, DNA polymerase, and an enzyme mixture that releases light by measuring the amount of pyrophosphate released when a nucleotide is incorporated into the primed DNA strand. Sequence analysis systems add the four-deoxynucleotide triphosphates one at a time and measures the light signals that result when nucleotides are incorporated. Primer flexibility is a key advantage of Pyrosequencing. A potential challenge for customers is a SNP in a difficult location. However, with Pyrosequencing we can place our primer wherever it's optimal relative to the SNP, up to 30 nucleotides away. They are always able to design primers for assays (Wygant, 2002).

The genotyping and detection of single nucleotide polymorphisms are very easily facilitated by Light-Cycler. According to Alderborn (2000), the device monitors the temperature dependent hybridization of the sequence specific hybridization probes to ss-DNA. After the amplification of a DNA fragment, amplicons are detected by the fluorescence using specific pairs of hybridization probes. After hybridization to the template DNA, the two probes come in close proximity, resulting in fluorescence resonance energy transfer (FRET) between the two fluorophores. During the FRET, released fluorescence of the Light Cycler fluorophore is measured (Suzanne, 2000).

New Challenges

Although selective breeding has improved livestock to a greater extent, we are facing several new challenges that require now changes both in the pace and direction of approaches for improvement. First, little genetic improvement has been achieved in some important traits either because they are expensive to measure (e.g. feed conversion efficiency in cattle) or because genetic variation in them are reported to be low (e.g. fertility) or has been largely ignored (Pryce *et al.,* 2002). In some traits, such as fertility of dairy cattle, genetic changes have been negative, largely because of negative correlation between production and reproduction traits. Genetic variation in heat stress response has been observed in livestock species where this has been measured, including dairy cattle and pigs (Hayes *et al.,* 2013). It is often reported to be tough to improve such traits by classical breeding approaches.

Advantages of SNP

SNPs are prevalent and provide more potential markers near or in any locus of interest than other types of polymorphism such as microsatellites. Some SNPs are located in coding regions and directly affect protein functions. These SNPs may be directly responsible for some of the variations among individuals in important traits. SNPs are more stably inherited than microsatellites, making them more suited as long-term selection markers. High throughput genetic analysis is more suitable for SNPs than microsatellites by

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the use of DNA microarray technology (Lipshutz *et al.*, 1999). SNPs are useful in identifying candidate genes that contribute to disease and phenotypic traits. They are numerous and widely distributed throughout the entire genome (Primmer *et al*., 2002). They have high genetic stability, excellent repeatability, high accuracy and also allow for fast, high-throughput genotyping (Tsuchihashi *et al.,* 2002). Convenient for effectively distinguishing heterozygote from homozygote alleles because of its co-dominances nature. Because of their extensive distribution and abundant variations, SNPs play an important role in farm animal population structure, genetic differentiation, origin and evolution research.

Limitation

SNPs will be of less use when compared to microsatellites with regard to evolution study, because the accumulation of new mutations (and an excess of rare alleles) requires longer time periods for slowly evolving loci. Another important problem is that what to do with large number of SNP studies with small number of samples? How it can be utilized? The relative usefulness of SNPs in comparison to other molecular markers is situation specific and more work is required to identify general rules, except in the cases of individual identification and parentage testing (Krawczak, 1999).

Conclusion

Dairy industry and farmers suffer a loss due to longer age at first calving, calving interval, service period, dry period of milch animals. For ensuring the higher dairy production, genetic improvements in reproductive trait of animals are needed. Generation intervals are reduced to drop from around 5 to 6 years in traditional dairy cattle breeding programs to around 1.5 years when using genetic markers. Many SNPs are located in genes which are associated with the reproductive traits. New SNPs genotyping methods are providing high density of SNPs. Reproduction traits determine productive life and culling decision of animals from herd.

SNPs are most common type of genetic variation. SNPs are rapidly becoming the marker of choice for many applications in population ecology, evolution and conservation genetics, because of their potential for higher genotyping efficiency, data quality, genome-wide coverage and analytical simplicity. The animals can be selected accurately, early in life using SNPs. Earlier methods of marker-assisted selection, were not successful for complex traits because most of these affected by hundred or thousand polymorphisms, each with small effects.

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DOI 10.5455/ijlr.20180227100002